Improving Risk Assessment Through the Use of Physiologically Based Models

Weihsueh Chiu
Environmental Health Scientist
Quantitative Risk Methods Group, National Center for Environmental Assessment
(202) 564-7789
chiu.weihsueh@epa.gov

Authors: Weihsueh Chiu, Chao Chen, Robert DeWoskin, Annie Jarabek, John Lipscomb, Allan Marcus, Ravi Subramaniam, Paul White

Key Words: pharmacokinetic model, quantitative risk assessment, human variability, species extrapolation, life stages

Mechanistic models, based on an organism's physiology, are increasingly used in risk assessment to improve our understanding of how chemicals are absorbed and distributed throughout the body. In the past, risk assessors would evaluate the potential for an adverse health effect based upon the environmental exposure or intake of an environmental toxicant. The same external exposure or intake, however, may not result in the same effect or response in different species or even among individuals within the same population. One contributor to these differences is the "kinetics" or movement of the chemical through the body. A chemical's so-called "pharmacokinetics" encompasses its absorption into the body, distribution throughout various tissues, metabolism into other chemical species, and subsequent excretion from the body. Differences in pharmacokinetics can result in different amounts of chemical ultimately reaching the site where the chemical is biologically active.

Physiologically based pharmacokinetic (PBPK) and dosimetry models are mathematical descriptions of an organism's physiology and how chemicals are absorbed, distributed, metabolized, and excreted in organs and tissues. With the appropriate data and biological information, they can therefore model a chemical's "internal dose"—the amount of chemical that actually reaches the site where it is biologically active. These models have been developed for a wide range of chemicals including organic compounds, pesticides, and heavy metals, and have a variety of applications, including (1) predicting or relating internal doses across different routes of exposure, different species, and different age groups or genders; (2) characterizing the variability in internal dose within a population; (3) reducing uncertainty in default assumptions; (4) predicting responses from exposure to mixtures of chemicals; and (5) integration with biologically based dose-response models that describe biological interactions with internal dose.

The National Center for Environmental Assessment, in collaboration with other ORD offices and outside scientists, is developing, evaluating, and using PBPK and dosimetry models for application to risk assessment. Ongoing efforts include (1) a report on the use of PBPK models in risk assessment, including illustrative case studies; (2) development of standardized, peer-reviewed parameter values across life stages; (3) increased use of PBPK and dosimetry models in risk assessments, including peer review of existing models, and development of new or modified models; (4) training on use of models for EPA and non-EPA risk assessors; and (5) developing and maintaining databases of PBPK and dosimetry models and available modeling resources.

Ultimately, it is expected that the use of PBPK and dosimetry models will strengthen the scientific basis of EPA risk assessments by improving the accuracy and completeness of quantitative estimates of risk by accounting for differences in internal dose.